PATENT SPECIFICATION

Inventor: RICHARD NORMAN LACEY

699,812

Date of filing Complete Specification Nov. 2, 1951.

Application Date Nov. 29, 1950. No. 29158/50.

Complete Specification Published Nov. 18, 1953.

Index at acceptance :—Class 2(iii), C2b4, C3a14a(3a: 8c), C3c5.

COMPLETE SPECIFICATION

Manufacture of Substituted Pyrimidones

SPECIFICATION NO. 699,812

INVENTOR:- RICHARD NORMAN LACEY

By a direction given under Section 17(1) of the Patents Act 1949 this application proceeded in the name of The Distillers Company Limited, a British company, of 12, Torphichen Street, Edinburgh 3, Scotland.

THE PATENT OFFICE,
21st October, 1953

DB 35955/1(8)/3517 150 10/53 R

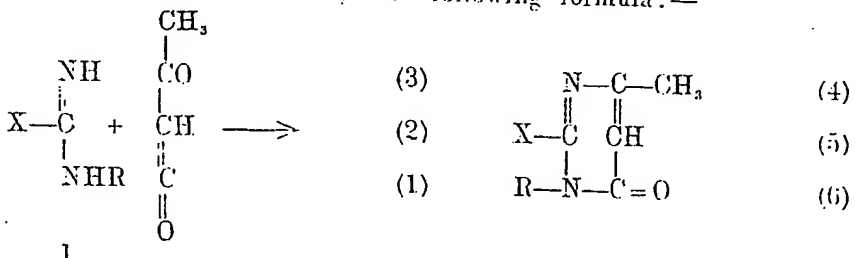
radical, R^1 may be hydrogen or an alkyl radical and R^2 may be an alkyl radical.

As suitable starting materials falling within the above formula may be mentioned amidines, for example acetamidine, propionamidine, benzamidine, N-methyl benzamidine ($R=CH_3$, $X=C_6H_5$), and phenylacetamidine ($R=H$, $X=C_6H_5(CH_2-)$. guanidines, for example guanidine, methyl guanidine ($R=CH_3$, $X=NH_2$). NN'-dimethyl guanidine ($R=CH_3$, $X=NHCH_3$) phenyl guanidine ($R=C_6H_5$. $X=NH_2$). and NN'-methyl phenyl guanidine ($R=C_6H_5$, $X=NHCH_3$) and isothioureas, for example S-methyl isothiourea ($R=H$, $X=-S.CH_3$). S-ethyl isothiourea ($R=H$, $X=-S.C_2H_5$). N-phenyl-S-methyl isothiourea ($R=C_6H_5$, $X=-S.CH_3$), N-phenyl-S-ethyl isothiourea ($R=C_6H_5$, $X=-S.C_2H_5$). and N-methyl-S-ethyl isothiourea ($R=CH_3$, $X=-S.C_2H_5$).

The amino compound starting materials are often available in the form of their salts, such as the hydrohalides or sulphates, and may be used as such, the its use is contraindicated if the starting material is insoluble in water or likely to be hydrolysed in the presence of water, as is the case with some of the lower aliphatic amidines. Organic solvents which are suitable include the commonly used organic solvents such as alcohols, for example methyl alcohol and ethyl alcohol, ethers, for example ethyl ether, isopropyl ether and dioxan, esters, for example ethyl acetate, ketones, for example acetone and methyl ethyl ketone, aromatic hydrocarbons, for example benzene and toluene, and chlorinated hydrocarbons for example chloroform, carbon tetrachloride and tetrachlorethane.

The reaction is suitably carried out at or about room temperature, such as at temperatures in the range $-10°$ C. to $60°$ C. If desired however, higher or lower temperatures may be used. The substituted pyrimidone produced may be separated from the reaction product in any suitable way.

The process of the present invention may be represented, for example by the following formula:—



(3) (2) (1) (4) (5) (6)

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COMPLETE SPECIFICATION

Manufacture of Substituted Pyrimidones

We, BRITISH INDUSTRIAL SOLVENTS LIMITED, a British Company, of 21, St. James's Square, London, S.W.1, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to an improved process for the manufacture of substituted pyrimidones which comprises reacting diketene with an amino compound of the formula $NH=CX—NHR$ where X may be an alkyl or aryl group, an $—NHR^1$ or $—SR^2$ group, wherein R may be hydrogen, an alkyl or aryl radical, R^1 may be hydrogen or an alkyl radical and R^2 may be an alkyl radical.

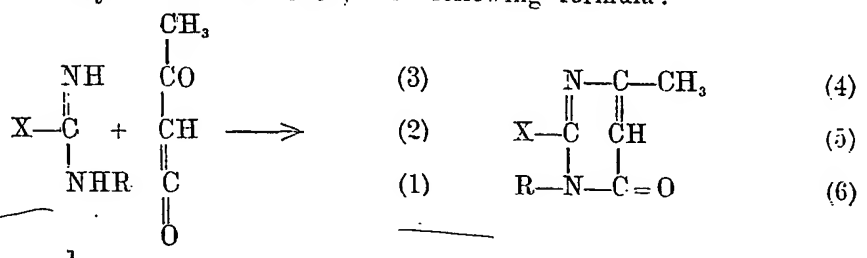
As suitable starting materials falling within the above formula may be mentioned amidines, for example acetamidine, propionamidine, benzamidine, N-methyl benzamidine ($R=CH_3$, $X=C_6H_5$), and phenylacetamidine ($R=H$, $X=C_6H_5CH_2—$), guanidines, for example guanidine, methyl guanidine ($R=CH_3$, $X=NH_2$), NN^1-dimethyl guanidine ($R=CH_3$, $X=NHCH_3$) phenyl guanidine ($R=C_6H_5$, $X=NH_2$), and NN^1-methyl phenyl guanidine ($R=C_6H_5$, $X=NHCH_3$) and isothioureas, for example S-methyl isothiourea ($R=H$, $X=—S.CH_3$), S-ethyl isothiourea ($R=H$, $X=—S.C_2H_5$), N-phenyl-S-methyl isothiourea ($R=C_6H_5$, $X=—S.CH_3$), N-phenyl-S-ethyl isothiourea ($R=C_6H_5$, $X=—S.C_2H_5$), and N-methyl-S-ethyl isothiourea ($R=CH_3$, $X=—S.C_2H_5$).

The amino compound starting materials are often available in the form of their salts, such as the hydrohalides or sulphates, and may be used as such, the reaction then being carried out in the presence of an alkaline material in order to liberate the free base. Alternatively, the free base *per se* may be employed.

The reaction can suitably be carried out by adding diketene, with stirring and, if necessary, cooling to a solution of the amino compound. The order or manner of admixture of the reactants is not in any way critical. It has been found desirable to carry out the reaction in a diluent medium which should be a solvent for the amino compound starting material, such as aqueous, aqueous organic solvent or organic solvent media. Water may frequently be used as the reaction solvent, although its use is contraindicated if the starting material is insoluble in water or likely to be hydrolysed in the presence of water, as is the case with some of the lower aliphatic amidines. Organic solvents which are suitable include the commonly used organic solvents such as alcohols, for example methyl alcohol and ethyl alcohol, ethers, for example ethyl ether, isopropyl ether and dioxan, esters, for example ethyl acetate, ketones, for example acetone and methyl ethyl ketone, aromatic hydrocarbons, for example benzene and toluene, and chlorinated hydrocarbons for example chloroform, carbon tetrachloride and tetrachlorethane.

The reaction is suitably carried out at or about room temperature, such as at temperatures in the range $-10°$ C. to $60°$ C. If desired however, higher or lower temperatures may be used. The substituted pyrimidone produced may be separated from the reaction product in any suitable way.

The process of the present invention may be represented, for example by the following formula:—



(1) (2) (3) (4) (5) (6)

[1]

The nomenclature of the substituted pyrimidones followed in the specification is as indicated in the formula above. The process of the present invention, particularly when the amino compound starting material is an isothiourea, is suitably carried out in the presence of an alkaline material. In those cases where the amino compound starting material is an isothiourea it has been found that direct formation of the substituted pyrimidone product does not always occur, an intermediate compound apparently being formed which is converted to the final pyrimidone product. Although the reaction in these cases may proceed to completion in the absence of alkaline material it has been found that the presence of alkaline material assists the rapid conversion of said intermediate compound into the substituted pyrimidone product. The alkaline material employed may be an alkali or alkaline earth metal hydroxide, or an organic base or other material of alkaline action, and is preferably an alkali metal hydroxide.

The alkylmercaptopyrimidones prepared according to the present invention may be hydrolysed into the corresponding uracil and mercaptan.

The following examples are given to illustrate the process of the present invention. The parts referred to in the Examples are by weight.

EXAMPLE 1

8.9 parts of diketene (95% purity by weight) is added to an agitated mixture of 19.25 parts of benzamidine hydrochloride dihydrate in a solution of 4 parts of sodium hydroxide in 50 parts of water, maintained at a temperature below 12°—13° C. On completing the addition the product is allowed to stand at room temperature for about half-an-hour and then filtered giving 12 parts of 2-phenyl-4-methyl - 6 - pyrimidone (melting point 214° C.) as a pale yellow crystalline solid. Crystallisation from alcohol gave the pure pyrimidone, melting point 223° C.

EXAMPLE 2

8.9 parts of diketene (95% purity by weight) is added to an agitated mixture of 12 parts of benzamidine in 50 parts of water maintained at a temperature of 12°—13° C. On completing the addition, the product is allowed to stand at room temperature for about half-an-hour and then filtered giving 13 parts of 2-phenyl-4-methyl-6-pyrimidone (melting point 214° C.). as a pale yellow crystalline solid.

EXAMPLE 3

A solution of 8 parts of sodium hydroxide in 25 parts of water is added to an agitated suspension of 18 parts of guanidine carbonate in 25 parts of water giving a pale yellow solution. 17.5 parts of diketene (94% purity by weight) are then added to the solution with stirring over 30 minutes at a temperature of 15°—20° C., and the stirring continued for one hour. The product obtained is filtered giving 3.5 parts of 2-amino-4-methyl - 6 - pyrimidone (melting point 285° C. with decomposition) in the form of white needle crystals.

EXAMPLE 4.

18 parts of diketene (94% purity by weight) is added dropwise to an agitated cooled solution of 19 parts of guanidine hydrochloride in a solution of 8 parts of sodium hydroxide in 50 parts of water at a temperature of 0—10° C., and on completing the addition the mixture is stirred at 20° C. for one hour and then allowed to stand at room temperature for 12 hours. The product is filtered giving 7 parts of 2-amino-4-methyl-6-pyrimidone (melting point 285°—290° C. with decomposition).

EXAMPLE 5

19 parts of thiourea, 38 parts of methyl iodide and 79 parts of ethyl alcohol are refluxed together for 2 hours and then the ethyl alcohol distilled off leaving S-methyl isothiouronium iodide.

55 parts of S-methyl isothiouronium iodide are dissolved in a solution of 10 parts of sodium hydroxide in 100 parts of water, and 22 parts of diketene (98% purity by weight) are added to this solution, with agitation, at a temperature below 6° C. The product is allowed to stand for 12 hours and is then filtered giving 24.6 parts of 2-methylmercapto-4-methyl-6-pyrimidone (melting point 219° C.).

EXAMPLE 6

A solution of 4.6 parts of sodium in ethyl alcohol (forming sodium ethoxide) is added to a solution of 19 parts of acetamidine hydrochloride in 78.5 parts of ethyl alcohol, the temperature being maintained below 5° C. 17.5 parts of diketene are then added to the solution with cooling and agitation and the product allowed to stand. The product is then filtered and the filtrate evaporated to small bulk giving 8.6 parts of 2:4-dimethyl-6-pyrimidone (melting point 201° C.).

EXAMPLE 7

8.6 parts of diketene are added to a solution of 16.7 parts of N-phenyl S-

methyl isothiourea in 39 parts of ethyl alcohol, the temperature of the solution being maintained below 40° C. The product is stirred for half an hour, after which time the product is concentrated, water and 5 parts of N-aqueous potassium hydroxide are added thereto and then the hot solution allowed to crystallise. 15 parts of 2-methylmercapto-1-phenyl-4-methyl-6-pyrimidone (melting point 148° C.) are thus obtained.

EXAMPLE 8

8.6 parts of diketene are added to a solution of 16.7 parts of N-phenyl S-methyl isothiourea in 108 parts of ether, the temperature of the solution being maintained below 40° C. The product is stirred for half an hour after which time the product is concentrated, water added thereto and the hot solution allowed to crytallise. 16 parts of a solid of the empirical formula $C_{12}H_{14}O_2N_2S$ (melting point 118° C.) separates which is rapidly converted in the presence of alkali to 2-methylmercapto - 1 - phenyl - 4 - methyl-6-pyrimidone.

EXAMPLE 9

The process of Example 8 is repeated using successively chloroform, acetone, dioxan, benzene and ethyl acetate in place of the ether employed therein, substantially the same yields of 2-methylmercapto - 1 - phenyl - 4 - methyl - 6 - pyrimidone being obtained.

EXAMPLE 10

4.3 parts of diketene are added with cooling and stirring to a solution of 11.6 parts of N:S-dimethyl isothiouronium iodide in 50 parts of N-aqueous sodium hydroxide. On completion of the addition, the stirring is continued for half an hour after which time 15 parts of 10% by weight aqueous sodium hydroxide are added giving 2.6 parts of 2-methylmercapto-1:4-dimethyl-6-pyrimidone melting point 90° C.). Crystallisation from water gave the pure pyrimidone, melting point 94° C.

On repeating the process of this example omitting the second addition of alkali, the formation of the pyrimidone is found to be delayed, and it only separates on standing for some days.

EXAMPLE 11

A solution of 4 parts of sodium hydroxide in 10 parts of water is added to a cooled, agitated solution of 11 parts of methyl guanidine hydrochloride in 50 parts of water, and then 8.8 parts of diketene are added to the solution, the temperature being maintained at 0°—10° C. The product is allowed to stand for 12 hours and is then concentrated, giving on cooling 1.1 parts of 1:4-dimethyl-2-amino-6-pyrimidone (melting point 310° C.).

EXAMPLE 12

A solution of 2.3 parts of sodium in 40 parts of ethyl alcohol is added to a solution of 20.6 parts of methyl benzamidine hydrochloride in 78.5 parts of ethyl alcohol. The precipitated sodium chloride is removed and the remaining solution is treated with 8.8 parts of diketene at 20° C. The product is allowed to stand for two days and is then distilled to remove the ethyl alcohol. 7 parts of 1:4 dimethyl-2-phenyl-6-pyrimidone, melting point 87—9° C. are obtained.

The products of the present invention are of utility in the chemical industry and may, for example, find application as intermediates in the production of valuable chemical compounds and as therapeutic agents.

What we claim is: —

1. A process for the manufacture of substituted pyrimidones which comprises reacting diketene with an amino compound of the formula: NH=CX—NHR where X is an alkyl or aryl group or an —NHR^1 or —SR^2 group, wherein R may be hydrogen or an alkyl or aryl radical, R^1 may be hydrogen or an alkyl radical and R^2 may be an alkyl radical.

2. A process as claimed in claim 1, wherein the reaction is carried out in the presence of an alkaline material.

3. A process as claimed in claim 2, wherein the alkaline material is an alkali metal hydroxide.

4. A process as claimed in any of the preceding claims, wherein the reaction is carried out in a diluent medium which is a solvent for the amino compound starting material.

5. A process as claimed in claim 4, wherein the diluent medium is water or an organic solvent.

6. A process as claimed in any of the preceding claims, wherein the reaction is carried out at a temperature in the range −10° C. to 60° C.

7. A process as claimed in any of the preceding claims, wherein the amino compound is acetamidine, propionamidine, benzamidine, N-methyl benzamidine or phenylacetamidine.

8. A process as claimed in any of the preceding claims 1—6 wherein the amino compound is guanidine, methyl guanidine or phenyl guanidine.

9. A process as claimed in any of the preceding claims 1—6, wherein the amino compound is S-methyl isothiourea, S-ethyl isothiourea, N-phenyl-S-methyl-

isothiourea, N-phenyl-S-ethylisothiourea, or N-methyl-S-ethylisothiourea.

10. A process for the manufacture of substituted pyrimidones substantially as hereinbefore described with reference to the Examples.

11. Substituted pyrimidones when prepared by the process of any of the preceding claims.

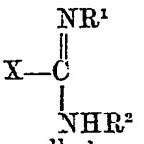
N. F. BAKER,
Agent for the Applicant.

PROVISIONAL SPECIFICATION

Manufacture of Substituted Pyrimidones

We, BRITISH INDUSTRIAL SOLVENTS LIMITED, a British Company, of 21, St. James's Square, London, S.W.1, do hereby declare this invention to be described in the following statement:—

The present invention relates to an improved process for the manufacture of substituted pyrimidones which comprises reacting an amino compound of the formula



where X may be an alkyl or aryl group, an —SR^3 or —NHR^4 group, where R^1, R^2, R^3 and R^4 may each be hydrogen or an alkyl or aryl radical, with diketene in a diluent medium, and recovering the substituted pyrimidone from the reaction product.

As suitable starting materials falling within the above formula may be mentioned amidines, for example benzamidine, guanidines, for example guanidine, and pseudothioureas, for example S-methyl isothiouronium halides. The reaction is suitably carried out in an aqueous medium at or about room temperature. The amino-compound starting materials are generally available in the form of their salts, such as the hydrochlorides, and may be used as such, the reaction suitably being carried out in an aqueous or aqueous-alcoholic alkaline medium to liberate the free base. Alternatively the amino-compound *per se* may be employed.

The reaction can suitably be carried out by adding diketene, with stirring, to an aqueous solution of the amino-compound, at or about room temperature. The order or manner of admixture of the reactants is not in any way critical.

The following examples are given to illustrate the process of the present invention. The parts referred to in the examples are by weight.

EXAMPLE 1

8.9 parts of diketene (95% purity by weight) is added to an agitated mixture of 19.25 parts of benzamidine hydrochloride dihydrate in a solution of 4 parts of sodium hydroxide in 50 parts of water, maintained at a temperature below 12°—13° C. On completing the addition the product is allowed to stand at room temperature for about half-an-hour, and then filtered giving 12 parts of 2-phenyl-4-methyl-5-pyrimidone (melting point 214° C.) as a pale yellow crystalline solid.

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EXAMPLE 4

18 parts of diketene (94% purity by weight) is added dropwise to an agitated cooled solution of 19 parts of guanidine hydrochloride in a solution of 8 parts of sodium hydroxide in 50 parts of water at a temperature of 0—10° C., and on completing the addition the mixture is stirred at 20° C. for one hour and then allowed to stand at room temperature for 12 hours. The product is filtered giving 7 parts of 2-amino-4-methyl-5-pyrimidone (melting point 285—290° C. with decomposition).

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The products of the present invention are of utility in the chemical industry and may, for example, find application as intermediates in the production of valuable chemical compounds and as therapeutic agents.

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Agent for the Applicants.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1953.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained